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EXAMINER	
EINSMANN, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/747,391	Applicant(s) CHOW ET AL.	
	Examiner Juliet Einsmann	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *6-9,20-22 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10-19,23-26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

4. The specification contains a number of tables after the abstract (see pages 48-78). These should be placed at some location before the claims, and the pages of the specification should be renumbered appropriately.

Appropriate correction is required.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): Pages 48-55 recite a multitude of sequences that are not identified with proper sequence identifiers.

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit, **as appropriate**, a new CRF including the sequences on pages 48-55, and paper copy of the Sequence Listing containing these sequences, in addition to the previously listed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 11 and 12 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 12 are indefinite insofar as they encompass the use of SEQ ID NO: 277 as a capture probe because it is not clear from the specification or the claims how SEQ ID NO: 277 can be used as a capture probe in the instant methods. From the results of a thorough sequence search, SEQ ID NO: 277 does not appear to be contained within any known HLA allele. The specification does not disclose what HLA alleles can be captured with this probe, and the prior art does not provide this information. Thus, it is unclear how SEQ ID NO: 277 can be used as a capture probe because it is unclear what will be captured by such a probe, as it is not clear what HLA allele will hybridize to SEQ ID NO: 277.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3, 4, 10, 14, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaneshige *et al.* (MHC & IRS, Supplement to Vol. 1, 1994, pages 159-164).

Kaneshige *et al.* teach a method for identifying an HLA gentoype of a subject, the method comprising :

(a) obtaining a sample comprising a template nucleic acid from said subject (p. 159);

(b) amplifying said template nucleic acid with a plurality of HLA allele-specific forward primers and HLA allele-specific reverse primers to form amplification products, wherein said forward primers or reverse primers comprise a detectable label (p. 159);

(c) hybridizing said amplification products with a plurality of HLA locus-specific capture oligonucleotides immobilized on a solid phase to form a plurality of detectable complexes (p. 159-160); and

(d) detecting said detectable complexes to identify said HLA genotype of said subject (p. 159-160).

In the method of Kaneshige *et al.*, the template nucleic acid is genomic DNA isolated from blood samples (p. 159), the HLA genotype is a class II genotype, and the detectable label is the binding protein biotin. This rejection applies to claim 15 because claim 15 further limits the fluorescent moiety recited in claim 14, but claim 15 does not require that the detectable label be a fluorescent moiety.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 2, 3, 4, 5, 10, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nevinny-Stickel *et al.* (European Journal of Immunogenetics (1993 Oct) 20(5)419-427) in view of Kaneshige *et al.*

Nevinny-Stickel *et al.* teach a method for identifying an HLA gentoype of a subject, the method comprising :

(a) obtaining a sample comprising a template nucleic acid from said subject (p. 421);

(b) amplifying said template nucleic acid with a plurality of HLA allele-specific forward primers and HLA allele-specific reverse primers to form detectably labeled amplification products (p. 421);

(c) hybridizing said amplification products with a plurality of HLA locus-specific capture oligonucleotides immobilized on a solid phase to form a plurality of detectable complexes (p. 421); and

(d) immobilizing said detectable complexes on a solid phase (p. 421); and

(e) detecting said detectable complexes to identify said HLA genotype of said subject (p. 421).

Nevinny-Stickel *et al.* teach samples wherein the template nucleic acid is isolated from blood (p. 421). In the method of Nevinny-Stickel *et al.*, the template nucleic acid is genomic DNA, the solid phase is a microtiter plate, the HLA genotype is a class II genotype, and the detectable label is the binding protein digoxigenin. This rejection applies to claim 15 because claim 15 further limits the fluorescent moiety recited in claim 14, but claim 15 does not require that the detectable label be a fluorescent moiety.

The specification defines an "HLA-allele specific primer" as an oligonucleotide that hybridizes to nucleic acid variations that define or partially define that particular HLA allele. The primers used by Nevinny-Stickel *et al.* are considered to be within the scope of this definition because they are specific to the HLA-DRB locus, thus they hybridize to variations in HLA genes that define the alleles as being DRB alleles.

Nevinny-Stickel *et al.* do not teach methods in which the forward primers or reverse primers comprise a detectable label.

However, methods for labeling amplification products using primers that comprise a detectable label were routine in the art at the time the invention was made. For example, Kanshige *et al.* teach methods for amplification of genomic DNA from blood samples that utilized primers comprising the detectable label biotin (p. 159, Table 1). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted labeled primers for the labeled DIG-11-dUTP taught by Nevinny-Stickel *et al.* The ordinary practitioner would have been motivated to make such a modification in order to have provided an alternative method for labeling the amplification products utilized in the methods taught by Nevinny-Stickel *et al.*

12. Claims 16, 17, 18, 19, 22, 23, 25, and 26 rejected under 35 U.S.C. 103(a) as being unpatentable over Bunce *et al.* (Tissue Antigens, 1995 ; 46 :355-367) in view of Morris *et al.* (US 6017738).

Bunce *et al.* teach a method for identifying an HLA genotype of a subject, the method comprising:

(a) isolating template nucleic acid from a sample from said subject (p. 358);

(c) amplifying said template nucleic acid with a plurality of HLA-allele specific forward primers and a plurality of HLA-allele specific reverse primers to form amplification products (p. 358); and

(d) detecting said amplification products to identify said HLA genotype of said subject (p. 361).

The template nucleic acid in the methods of Bunce *et al.* is genomic DNA isolated from blood (p. 358). Bunce *et al.* determine HLA class II genotypes.

Bunce *et al.* do not teach methods in which the HLA allele-specific reverse primers are immobilized or in which the forward primers are labeled.

Morris *et al.* teach a method of solid phase amplification (SPA) the method comprising:

(b) immobilizing a plurality of reverse primers on a solid phase (Col. 7, line 50);

(c) amplifying said template nucleic acid with a plurality of forward primers and said immobilized reverse primers to form amplification products (Col. 7, lines 51-55), wherein said forward primers comprise a detectable label (Col. 7, line 51); and

(d) detecting said amplification products (Col. 7, lines 55-57)

Morris *et al.* specifically teach that their method can be used to identify HLA genotypes (Col. 3, line 47). Furthermore, Morris *et al.* teach that the in a preferred embodiment the solid phase is the side of a microtiter well (Col. 4, lines 20-22). Morris *et al.* teach that the immobilized reverse primers comprise a 5' amine group (Col. 5-6). Morris *et al.* teach methods wherein the detectable label is a fluorescent moiety, particularly wherein the fluorescent moiety is fluorescein (Col. 9, lines 55-59).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Bunce *et al.* so as to have used the solid phase amplification methods taught by Morris *et al.* The ordinary practitioner would have been motivated to make such a substitution in order to have taken advantage of the many benefits of the SPA methods taught by Morris *et al.* For example, Morris *et al.* clearly motivate the use of their method when they teach "Of relevance here is the intrinsic high level of amplicon containment offered by solid phase amplification (SPA). SPA requires very little manipulation of solution phase amplicons. Such amplicons are removed from SPA reactions by simple washes and can be readily destroyed. Additionally, the solid phase amplicons offer little or no contamination threat. The level of containment is unmatched by any other amplification process. Thus SPA offers a high degree of amplicon containment (Col. 2, lines 55-63)."

13. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kaneshige *et al.* in view of Allen *et al.* and further in view of Erlich *et al.* (European Journal of Immunogenetics (1991), 18, 33-55).

Applicant elected for prosecution in claim 11 the primer pair consisting of SEQ ID NO: 192 and SEQ ID NO: 222.

Kaneshige *et al.* teach a method for identifying an HLA gentoype of a subject, the method comprising :

(a) obtaining a sample comprising a template nucleic acid from said subject (p. 159);

(b) amplifying said template nucleic acid with a plurality of HLA allele-specific forward primers and HLA allele-specific reverse primers to form amplification products, wherein said forward primers or reverse primers comprise a detectable label (p. 159);

(c) hybridizing said amplification products with a plurality of HLA locus-specific capture oligonucleotides immobilized on a solid phase to form a plurality of detectable complexes (p. 159-160); and

(d) detecting said detectable complexes to identify said HLA genotype of said subject (p. 159-160).

Primer R86A taught by Kaneshige *et al.* comprises SEQ ID NO: 222. The primer taught by Kaneshige *et al.* differs from instant SEQ ID NO: 222 because it has an additional nucleotide at the 5' end of the primer.

Kaneshige *et al.* do not teach a primer consisting of SEQ ID NO: 222, nor do they teach a primer consisting of SEQ ID NO: 192.

Allen *et al.* teach methods which utilize HLA allele specific primers. Primer UG 116 taught by Allen *et al.* comprises instant SEQ ID NO: 192. The primer taught by Allen *et al.* differs from SEQ ID NO: 192 because it has an additional nucleotide at the 5' end and two additional nucleotides at the 3' end.

Erlich *et al.* provide an alignment of the nucleotide sequences of DRB1 HLA class II alleles. Instant SEQ ID NO: 192 is contained within the sequences disclosed for alleles 1501, 1502, 1601, and 1602 (p. 48, beginning with the third nucleotides in these sequences). Instant SEQ ID NO: 222 is the complement of a portion of the sequences disclosed for alleles 1601 and 1602 (p. 50, second nucleotide of codon 85 through the second nucleotide of codon 92). The nucleotides that are added to SEQ ID NO: 192 and SEQ ID NO: 222 in the teachings of Kaneshige *et al.* and Allen *et al.* are nucleotides that are conserved within the respective alleles that these primers are directed towards. For example, the additional one nucleotide added onto

the 5' end of SEQ ID NO: 222 is conserved throughout all HLA DRB1 alleles disclosed by Erlich *et al.* The additional nucleotides that are in the primer taught by Allen *et al.* are conserved within the four alleles that SEQ ID NO: 192 is contained within.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the primer taught by Allen *et al.* in the methods taught by Kaneshige *et al.* The ordinary practitioner would have been so motivated in order to provide an additional method for allele specific amplification of HLA alleles, as Allen *et al.* specifically teach that this primer is specific for alleles 1501-1503 and 1601-1602. The modification of the primers in the prior art by the removal of nucleotides is a prima facie obvious modification. The removal of nucleotides from nucleic acid probes and primers is matter of routine optimization in the art, as is exemplified by the teachings of Kaneshige *et al.* who disclose the modification of oligonucleotide probes by both shortening and lengthening. Combined with the teachings of Erlich *et al.* who provide the full nucleotide sequence of the target alleles, the ordinary practitioner would have been motivated to modify the primers taught by Kanshige *et al.* and Allen *et al.* in order to provide equivalent primers for allele specific amplification of nucleic acid sequences.

14. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlich *et al.*

Applicant elected SEQ ID NO: 277 for prosecution in claims 11 and 12. This sequence is free of the prior art. Thus, an alternate sequence has been searched and examined.

Erlich *et al.* teach a method for identifying an HLA gentoype of a subject, the method comprising :

(a) obtaining a sample comprising a template nucleic acid from said subject;

(b) amplifying said template nucleic acid with a plurality of HLA allele-specific forward primers and HLA allele-specific reverse primers to form amplification products, wherein said forward primers or reverse primers comprise a detectable label;

(c) hybridizing said amplification products with a plurality of HLA locus-specific capture oligonucleotides immobilized on a solid phase to form a plurality of detectable complexes; and

(d) detecting said detectable complexes to identify said HLA genotype of said subject (see, for example, figure 1). The capture oligonucleotide in the methods taught by Erlich *et al.* comprise a 5' poly-T sequence.

Erlich *et al.* provide an alignment of the nucleotide sequences of DRB1 HLA class II alleles, including the DQB1 alleles (p. 44-45). The capture probe instantly disclosed as SEQ ID NO: 274 is contained within HLA DQB1*0301, DQB1*0301, and DQB1*0301 (see section encoding amino acids 35-43).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have selected an additional capture probe from the sequence alignment provided by Erlich *et al.*, as Erlich *et al.* teach that "Additional primers and/or probes can, of course, increase the allelic discrimination of oligonucleotide dot blot typing (p. 33)." The ordinary practitioner would have been motivated to select instant SEQ ID NO: 274 due to its specificity to the DQB1*03 alleles.

15. Claims 24 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bunce *et al.* (Tissue Antigens, 1995 ; 46 :355-367) in view of Morris *et al.* (US 6017738) as applied to

claims 16, 17, 18, 19, 22, 23, 25, and 26 above, and further in view of the combined teachings of Kaneshige *et al.*, Allen *et al.* and Erlich *et al.*

The teachings of Bunce *et al.* in view of Morris *et al.* are applied to these claims as they are applied in the previous rejection of claims 16, 17, 18, 19, 22, 23, 25, and 26.

Bunce *et al.* in view of Morris *et al.* do not teach allele specific primers consisting of SEQ ID NO: 192 and SEQ ID NO: 222.

Primer R86A taught by Kaneshige *et al.* comprises SEQ ID NO: 222. The primer taught by Kaneshige *et al.* differs from instant SEQ ID NO: 222 because it has an additional nucleotide at the 5' end of the primer.

Kaneshige *et al.* do not teach a primer consisting of SEQ ID NO: 222, nor do they teach a primer consisting of SEQ ID NO: 192.

Allen *et al.* teach methods which utilize HLA allele specific primers. Primer UG 116 taught by Allen *et al.* comprises instant SEQ ID NO: 192. The primer taught by Allen *et al.* differs from SEQ ID NO: 192 because it has an additional nucleotide at the 5' end and two additional nucleotides at the 3' end.

Erlich *et al.* provide an alignment of the nucleotide sequences of DRB1 HLA class II alleles. Instant SEQ ID NO: 192 is contained within the sequences disclosed for alleles 1501, 1502, 1601, and 1602 (p. 48, beginning with the third nucleotides in these sequences). Instant SEQ ID NO: 222 is the complement of a portion of the sequences disclosed for alleles 1601 and 1602 (p. 50, second nucleotide of codon 85 through the second nucleotide of codon 92). The nucleotides that are added to SEQ ID NO: 192 and SEQ ID NO: 222 in the teachings of Kaneshige *et al.* and Allen *et al.* are nucleotides that are conserved within the respective alleles

that these primers are directed towards. For example, the additional one nucleotide added onto the 5' end of SEQ ID NO: 222 is conserved throughout all HLA DRB1 alleles disclosed by Erlich *et al.* The additional nucleotides that are in the primer taught by Allen *et al.* are conserved within the four alleles that SEQ ID NO: 192 is contained within.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the primers taught by Kaneshige *et al.* and Allen *et al.* in the methods taught by Bunce *et al.* in view of Morris *et al.* The ordinary practitioner would have been so motivated in order to provide an additional method for allele specific amplification of HLA alleles. Furthermore, the modification of the primers in the prior art by the removal of nucleotides is a prima facie obvious modification. The removal of nucleotides from nucleic acid probes and primers is matter of routine optimization in the art, as is exemplified by the teachings of Kaneshige *et al.* who disclose the modification of oligonucleotide probes by both shortening and lengthening. Combined with the teachings of Erlich *et al.* who provide the full nucleotide sequence of the target alleles, the ordinary practitioner would have been motivated to modify the primers taught by Kanshige *et al.* and Allen *et al.* in order to provide equivalent primers for allele specific amplification of nucleic acid sequences.

Conclusion

16. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C. Einsmann
Examiner
Art Unit 1634

June 14, 2002

W. Gary Jones
Supervisory Patent Examiner
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